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Novel Synthesis of Difluoromethyl-Containing 1,4-Disubstituted 1,2,3-Triazoles *via* a Click–Multicomponent Reaction and Desulfanylation Strategy

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Abstract: Fourteen difluoromethyl-containing 1,4-disubstituted 1,2,3-triazoles were synthesized *via* a novel copper-catalyzed click-multicomponent reaction of 2,2-difluoro-2-phenylsulfanylethanol, sodium azide and terminal alkynes in the presence of *N*-(*p*-toluenesulfonyl)imidazole, tetrabutylammonium iodide and triethylamine, followed by reductive cleavage of the phenylsulfanyl group using tributyltin hydride and azobisisobutyronitrile.

Keywords: azides; click chemistry; desulfanylation; difluoromethyl group; multicomponent reactions

1,4-Disubstituted 1,2,3-triazole derivatives have found widespread applications in various different areas including bioconjugations, polymer, surface science, pesticides and pharmaceuticals.[1] The most popular method for the construction of the 1,2,3-triazole framework is the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition.[2] Multicomponent reactions have been proven to be a practical and efficient method to access complex structures from simple building blocks.[3] Compared to the classical step-by-step formation of individual bonds for the target compounds, multicomponent reactions (MCRs) take advantage of the simultaneous formation of several bonds in a single step. Recently, the combination of click chemistry and MCR (click–multicomponent reaction, CMR) has aroused great interest in the chemical community this is because the new reaction possesses the advantages of both click reaction and multicomponent reaction.[4] However, a survey of the literature revealed that there were only a few reports on the preparation of 1,2,3-triazole derivatives *via* click-MCR chemistry protocols.[5]

The development of difluoromethyl-containing scaffolds has gained a real interest especially in the organic and pharmaceutical areas due to their unique chemical and physiological properties.[6] It was reported that some 1,2,3-triazoles bearing a CF_2H unit exhibit herbicidal or protein kinase inhibitive bioactivity (Figure 1).[7] Up till now, several different methods for the preparation of CF_2H-containing compounds have been developed such as direct fluorination (using fluorine gas, hydrogen fluoride, fluorinating agents),[8] the usage of simple reactive fluoro-containing building blocks and the nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylations.[9] More recently, we reported a general and efficient synthesis strategy for the construction of the functionalized small molecules having a terminal CF_2H group.[10] In continuation of our interest in the synthesis of new difluoromethyl compounds, herein we report a concise and practical strategy for the synthesis of difluoromethyl-containing 1,4-disubstituted 1,2,3-triazole derivatives *via* a novel CuI-catalyzed click–multicomponent reaction based on fluoro-containing building blocks (CMR-FBB), followed by reductive cleavage of the phenylsulfanyl group (Scheme 1).

According to the literature, 1,4-disubstituted 1,2,3-triazoles can be prepared in excellent yields by the one-pot three-component 1,3-dipolar cycloaddition of

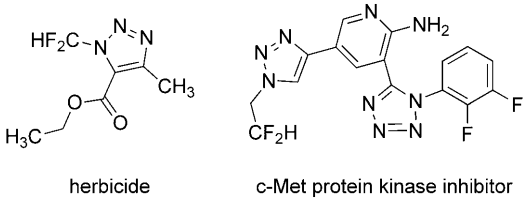
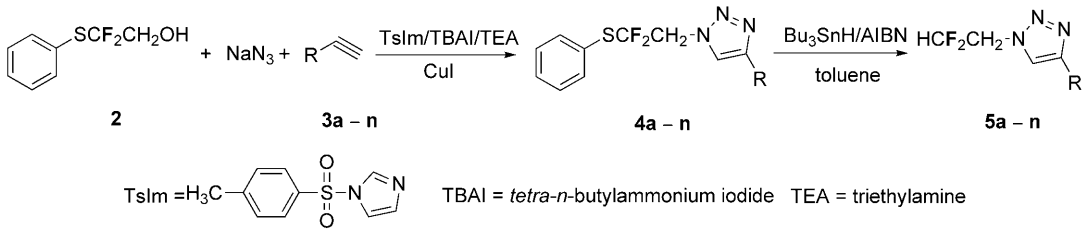
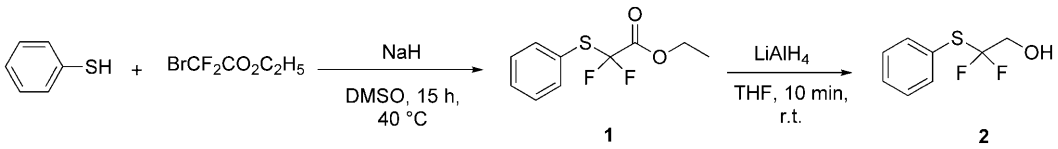


Figure 1. Two examples of bioactive 1,2,3-triazoles bearing a CF_2H group.



Scheme 1. Synthesis of CF_2H-containing 1,4-disubstituted 1,2,3-triazoles *via* a click–multicomponent reaction and desulfanylation strategy.



Scheme 2. Synthesis of 2,2-difluoro-2-phenylsulfanylethanol.

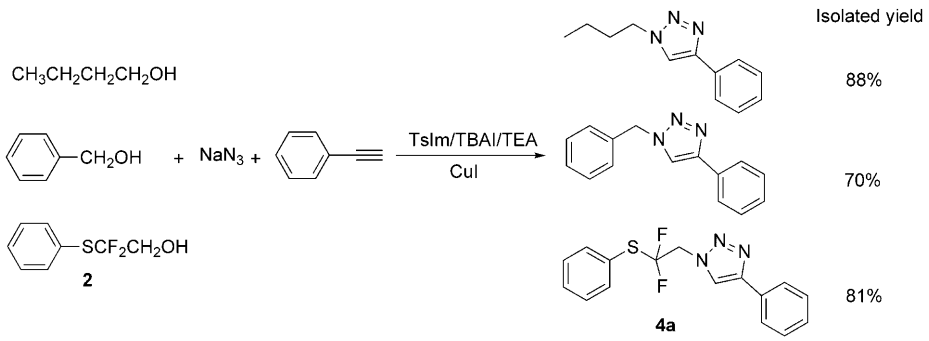
alkyl or aryl halides, sodium azide, and terminal alkynes.[11] Some other click–multicomponent reactions involved the use of organic azides as one of the components.[12] Compared to sodium azide, organic azides are relatively safe, however, some organic azides of low molecular weight could be unstable and hard to handle, thus, the search for an efficient method that avoids the isolation of organic azides is not only highly desirable but also necessary.

In this communication, we firstly designed and synthesized a novel difluoro-containing building block, 2,2-difluoro-2-phenylsulfanylethanol (**2**). The synthetic pathway for compound **2** is outlined in Scheme 2. The ethyl 2,2-difluoro-2-(phenylthio)acetate (**1**) was readily prepared by the reaction of ethyl bromodifluoroacetate and thiophenol according to the literature,[13] and the intermediate **1** could easily be reduced by $LiAlH_4$ to give corresponding alcohol **2**. It should be mentioned that the reaction time of the reduction should not exceed 10 min, otherwise, the hydrodefluorination takes place and a mixture of **2** and the defluorinated compound is obtained.[14]

With the new difluorinated building block which contains an inactive group (PhS) and a reactive group (OH) in hand, we turned our efforts to use it as one of the components to prepare the 1,4-disubstituted 1,2,3-triazoles *via* a three-component cycloaddition reaction. To the best of our knowledges, this is the first example of using an alcohol as substrate in the click–multicomponent reaction.

It is reported that the azide ion reacts with the tosylate to give the organic azide *via* nucleophilic substitution.[4] In order to avoid the isolation of unstable, toxic or sensitive organic azides and the use of expensive iodide, as a first step, we performed this one-pot click reaction of sodium azide and phenylacetylene with three different types of alcohols (1-butanol, phenyl methanol, 2,2-difluoro-2-phenylsulfanylethanol **2**) to check the potential and compatibility of copper(I) iodide as a catalyst in the TsIm/TBAI/TEA system using DMF as a solvent. To our delight, the reaction was found to be simple and efficient, giving the corresponding products 1,4-disubstituted 1,2,3-triazoles in good to high yields. (Scheme 3)

Generally, the catalyst plays a particularly important role in the click reaction. Therefore, 2,2-difluoro-2-phenylsulfanylethanol (**2**), sodium azide and phenylacetylene were selected as representative reactants



Scheme 3. The reactions of *n*-butyl alcohol, benzyl alcohol, **2** with sodium azide and phenylacetylene.

Table 1. Effect of catalysts on the one-pot reaction.

Catalyst[a]	Time [h]	Yield [%][b]
none	>12	0
CuCl	2	56
CuBr	2	70
CuI	1	81
$CuSO_4 \cdot 5H_2O$	>10	0

[a] 10 mmol% of catalysts were used.
[b] Isolated yield.

Table 2. Effect of temperature and time on the one-pot reaction.

Entry	Temperature [°C]	Time [h]	Yield[a] [%]
1	100	6	30
2	100	8	60
3	100	10	81
4	100	12	78
5	60	10	10
6	80	10	60
7	120	10	74
8	150	10	53

[a] Isolated yield.

Table 3. Effect of the amount of Bu_3SnH on the desulfanylation reaction.

Entry[a]	Bu_3SnH (equiv.)	Time [h]	Yield[b] [%]
1	1	3	59
2	1.5	3	71
3	2	1.5	89
4	3	0.7	92

[a] 10 mmol% of AIBN was used.
[b] Isolated yield.

for further investigation of the effect of the copper salt on this one-pot reaction. In the absence of the catalyst, the reaction could not proceed well even after a prolonged reaction time. Several other copper salts were screened in our model reaction and the results are shown in Table 1. It was found that CuI exhibited high catalytic activity in terms of reaction time as well as yields of the products. However, copper(II) sulfate pentahydrate had no observable catalytic effect on the reaction.

Using the same substrates, the effects of the reaction temperature and time were also examined in the presence of CuI. Generally, the yield was significantly affected by both reaction time and reaction temperature. As shown in Table 2, the reaction proceeded smoothly in DMF at 100 °C for 10 h, yielding the expected product in 81% yield. A further increase in temperature would lead to a decrease in yield and accelerate the formation of the by-product diphenyl disulfide.

Finally, in order to obtain 1,4-disubstituted 1,2,3-triazoles bearing a terminal difluoromethyl group, we attempted to remove the protecting group (PhS) using Bu_3SnH/AIBN as the reducing agent.[15] The removal of the PhS group from **4a** was used as a model reaction to investigate the effect of the amount of Bu_3SnH on the desulfanylation reaction. The results are listed in Table 3. We were delighted to find that the reaction proceeded much faster than other reported desulfanylations.[10,16] Treatment of **4a** with 3 equivalents of Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing toluene for only 40 min could afford desired product **5a** in 92% yield (entry 4).

To survey the generality and scope of the method, a variety of alkynes were examined under the optimized conditions (Table 4 and Scheme 1). In all cases, both the new click three-component reaction and desulfanylation proceeded smoothly to give the corresponding 1,4-disubstituted 1,2,3-triazoles bearing a terminal difluoromethyl group in good to high yields.

In summary, we have reported a novel and efficient protocol for the synthesis of CF_2H-containing 1,4-disubstituted 1,2,3-triazoles by a Cu(I)-catalyzed one-pot three-component reaction of $PhSCF_2CH_2OH$, sodium azide and terminal alkynes, followed by the cleavage of phenylsulfanyl group. We also provided a simple approach for the synthesis of 1,2,3-triazole derivatives from easily available alcohols. Furthermore, this new strategy, click–multicomponent reaction based on a fluoro-containing building block (CMR-FBB), will be a useful tool for one-pot synthesis of fluoro-containing 1,2,3-triazole derivatives with high efficiency.

Experimental Section

All reagents were of analytical grade, and were obtained from commercial suppliers and used without further purification. Toluene was dried by standard methods prior to use. Melting points were measured in an open capillary using a Büchi melting point B-540 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard, The ^{19}F NMR spectra were obtained using a Bruker AM-400 spectrometer (376 MHz). $CDCl_3$ was used as the NMR solvent in all cases except compound **5j**. Gas chromatography-mass spectra (GC-MS) were recorded on an HP 5973 MSD with a 6890 GC. High-resolution mass spectra (HR-MS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Compounds **1**,[13] **3e–k**,[17] **3l–n**[18] were synthesized according to literature procedures.

Table 4. Synthesis of 1,4-disubstituted 1,2,3-triazoles bearing terminal difluoromethyl group *via* click three-component reaction, followed by cleavage of the phenylsulfanyl group.

Entry	R	Yield[a] [%] of **4**	Yield[a] [%] of **5**
a	C_6H_5	81	92
b	*p*-$CH_3C_6H_4$	85	92
c	*m*-$CH_3C_6H_4$	84	91
d	*p*-$CH_3OC_6H_4$	82	88
e	$C_6H_5OCH_2$	80	87
f	*p*-$FC_6H_4OCH_2$	75	80
g	*o*-$CH_3C_6H_4OCH_2$	81	92
h	*p*-$CH_3C_6H_4OCH_2$	83	91
i	*p*-$(CH_3)_3CC_6H_4OCH_2$	82	90
j	4-CH_3-2,6-di-$(CH_3)_3CC_6H_2OCH_2$	84	89
k	(naphthalen-1-yloxy)methyl	80	85
l	$C_6H_5CONHCH_2$	75	80
m	*p*-$CH_3C_6H_4CONHCH_2$	78	82
n	3,5-di-$CH_3C_6H_3CONHCH_2$	76	84

[a] Isolated yield.

2,2-Difluoro-2-(phenylthio)ethanol (2)

A solution of the ethyl 2,2-difluoro-2-(phenylthio)acetate (**1**) (9.28 g, 40 mmol) in dry THF (40 mL) was added dropwise to a suspension of lithium aluminium hydride (2.28 g, 60 mmol) in dry THF (40 mL) at 0 °C under an argon atmosphere. The reaction mixture was then stirred at 0 °C for 10 min and quenched with H_2O (10 mL). The resulting suspension was stirred for 10 more minutes and filtered. The filtrate was diluted with ethyl acetate, washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to leave the crude product. The resultant crude residue was purified by chromatography to obtain compound **2** as yellow liquid; yield: 80%; GC-MS: $m/z = 190, 159, 110, 77$.

General Procedure for the Preparation of 4a–n

To a stirred solution of **2** (0.38 g, 2 mmol) in 10 mL DMF, TsIm (0.88 g, 4 mmol), sodium azide (0.38 g, 4 mmol), TBAI (0.03 g, 0.06 mmol), and TEA (0.58 mL,4 mmol) were added successively. The mixture was stirred for 10 h at 100 °C. Then, the mixture was cooled to room temperature, **3** (1.8 mmol) and CuI (0.04 g, 0.2 mmol) were added to the solution. The reaction was continued for 1–3 h (TLC), and quenched with H_2O (10 mL). The resulting suspension was filtered and the filtrate was diluted with CH_2Cl_2, washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure to leave the crude product. The resultant crude residue was purified by chromatography to give the pure product **4.**

General Procedure for the Preparation of 5a–n

To a solution of **4** (1 mmol) in dry toluene (5 mL) was added Bu_3SnH (0.87 g, 3 mmol) under an argon atmosphere. Deoxygenation was continued for 5 min. Azobisisobutryonitrile (AIBN) (0.02 g, 0.1 mmol) was added and the solution was heated at reflux for 40 min (TLC). The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (5 mL). The solution was stirred with KF/H_2O (15 mg/0.15 mL) for 4 h and extracted with EtOAc (15 mL × 3). The organic layer was washed successively with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. After solvent removal, the crude product was purified by chromatography to give desired product **5.**

Acknowledgements

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